Gottesman, Susan 2008 A

Dr. Susan Gottesman Oral History 2008 A

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NCI Laboratory of Molecular Biology

Oral History Project

Interview #1 with Dr. Susan Gottesman

Conducted on October 1, 2008, by Jason Gart

JG: My name is Jason Gart, and I am a senior historian at History Associates Incorporated in Rockville, Maryland. Today's date is October 1, 2008, and we are in the office of the National Institutes of Health in Bethesda,Maryland. Please state your full name and also spell it.

SG: Susan Gottesman. S-U-S-A-N—G-O-T-T-E-S-M-A-N.

JG: Terrific, thank you. Established in 1970, the Laboratory of Molecular Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, commonly known as LMB, currently has among its ten groups four members of the National Academy of Sciences. LMB has trained many other prominent scientists and its research has contributed both to basic science and to novel applied cancer treatments. LMB has initiated this oral history project to capture recollections of prominent scientists currently and formerly associated with the laboratory. Talk a little bit about where you were born, and also some of your interests as a child.

SG: I was born in Manhattan and my family moved to Long Island when I was in kindergarten, I guess, or maybe before that. I think I liked doing puzzles. I wouldn't say I was athletic; that was the opposite to what I was. I did a lot of reading of anything I encountered.

JG: What did your parents do?

SG: My father had gotten an accounting degree. They both came of age during the Depression. He got an accounting degree and when I was growing up was running a company that made rotisseries and other small appliances. My mother, for the most part, was working as a teacher. She taught typing and stenography in high school and then later became a guidance counselor and worked some of the time in my father's office. So depending on how the business was doing, sometimes she was working with him, but mostly was in high school, teaching high school.

JG: I read that you read as a young person a book by Paul de Kruif.

SG: Yes, *Microbe Hunters*. As I said, I read pretty much everything. My father on a regular basis would give me books that he had encountered or liked. Maybe my mother did too, but I don't remember those so much. I remember a number of the ones my father gave me. And one of them was this, was *Microbe Hunters*. I don't know how he encountered it, but that really captured my imagination. So I think I probably read that when I was in about sixth grade. I liked the science, how they had figured out that bacteria were doing things. It is also a book that is written with a great deal of drama so that the science sounds very dramatic. But I think it was really the logic of how you could dissect things out with bacteria that appealed to me and I became totally enamored of microbes.

JG: And, if I am correct, it describes the story of several scientists?

SG: That's right. It starts with the first people who could see bacteria in the microscope. Then it goes on to [Louis] Pasteur and how he figured out what bacteria caused what diseases and how people first started to isolate single colonies by streaking them out on potatoes. Then it goes on to development of vaccines and figuring out that microbes cause disease, first in yellow fever and various other things.

JG: So in sixth grade who was your favorite scientist in the book?

SG: I don't remember that I had one. So, none of them were women. [Laughs] Not that I think that occurred to me that this didn't fit me. I just assumed that it was fine. It was not that one of them personally appealed to me as a model. It was more the thought processes. So, I mean, [Robert] Koch and Pasteur were the ones who were doing how do you figure out, how do you get from A to B, how do you figure out that this is what is doing things. That is what appealed to me more than a person and what they had done, per se.

JG: What career do you think you would have pursued—

SG: If I had not encountered that? Well, hopefully I would have encountered some other science. I really enjoyed in high school a lot of the social studies courses that I took and thought a little bit about doing that in college as a major. The fact that I had actually been in a lab a little bit, in a high school summer program, meant I knew that I liked to play in the lab. I enjoyed the coursework in the social sciences but it was hard for me to imagine a career reading and writing entirely. So even though those courses were appealing, and the ideas were appealing, it was the science that really appealed to me. So I suspect I would have encountered maybe different science at a different stage. I think when I left high school I was also interested in physics to some extent until I met the real physicists in my starting courses at Harvard and realized that I was not in quite the same realm as some of them.

JG: For a second, go back and speak about the summer programs, and how you got involved in them?

SG: So basically having read that book . . . I think I did a science project in junior high on "Microbe Moe" which was this horrendous looking thing made out of contact paper—I'm not really good at those multimedia things—about how bacteria could come in and get out of the body. But I remained interested. Then there was an opportunity. I don't even remember how I learned about it, but midway through high school there were NSF summer programs, one of them at a place nearby on Long Island called Waldemar [Medical Research Foundation] which were meant for high school students interested in biology. I applied and got into that. I was in that for two summers. Part of it was lectures, but lectures at a high level, by really terrific high school teachers from around the area that came in and talked about what was going on. And what was going on was the discovery of DNA and what it did, which our high school biology course had not touched on. So there was a lot to learn. And then on the other hand there were projects. The first summer we may have been doing some things with mice, which I could do, but was not excited about. I think the second summer we were trying to get a bacteria to grow on a defined medium. The experiments were not sophisticated in retrospect. The place was a little odd. [Laughs] But as a place to be for the summer, with obviously a group of other students as well, and good teachers, it was lots of fun and reinforced my interests.

JG: Talk about—because I know you later have a connection with Watson—how you first learned about the discovery of DNA and what intrigued you by that?

SG: Well, I am not sure it had quite the impact, because I am not sure that they got into how the code works and how DNA was translated which is the really appealing part that I learned about in coursework when I was in college. But even the fact that we knew that that was the material of genes, I think I didn't know much before high school. I can't tell you that Watson as a person existed at all in my mind. When I did end up working him, it was partially because there was advertisement and it was a chance to work in a lab when I did not have anything else going on at that time. It was not that this is Watson and I should go work with him. It was just in a sense accidental.

JG: So in high school you decide to—

SG: The other thing that was going on, obviously, this is post-Sputnik, and so there was an emphasis on science and there were some pretty good science courses in my high school as well, advanced courses. So I was interested . . . I applied to college looking for a college where I could do science and where there would be pretty advanced science possibilities. So I applied to schools that had strong science for the most part.

JG: At that point, were your aspirations to be a physician or doctor?

SG: No, no. [Laughs] My mother's joke was, if she wanted a conversation to stop or she wanted me to walk away, she would say, "Why don't you be a doctor?" In fact, I did not have the personality or the interest in that part of it. I was interested in the puzzle solving at the bacterial level and I was not particularly social or did not see myself as having the interests or the skills to want to be a physician. It was not something my parents pushed. I think sometimes parents do push that because it is easier to visualize as a safe career. But maybe because I was a woman, they did not see that I had to have a career that was guaranteed. I do not know that any of us had a clear idea of what being a scientist meant long term. It was just; I was going to go do that.

JG: You wrote a fascinating line, and I am going to read it, because it touches on this. You wrote: "I had the wrong personality to deal with patients, not a great memory for facts unless I could fit them into a logical theory, no stomach for the messier aspects of medicine, and little family pressure to become a physician."

SG: Yes, pretty much. [Laughs]

JG: It is a great line. So expand on it a little bit. Do you think all of those things have to come together to be a physician? Is a lot of it a great memory for facts, the stomach for the messier aspects of medicine. Is family pressure important?

SG: Well, no. I am speaking always from personal experience to some extent. My husband is an M.D., my daughter is an M.D. They are both, I consider, much more social than I am. They are much more comfortable walking up to somebody and starting a conversation, finding out about them. That is not something that I am particularly comfortable doing or ever wanted to do. Family pressure comes or goes. There were lots of people who have family pressure to be a doctor, but do not do it, and plenty of people who do it without family pressure. I certainly see students coming through the lab where their idea of what they can do is directed by family pressure. Yes, maybe I am a little squeamish. I don't know. Those are things people get used to—but there was no reason to get used to it. As I said, we worked with mice one year in the lab. I could handle it. The first few times your hand shakes picking up this mouse and doing things to it, but I got used to that. I suspect I could adjust to that. But what I was interested in was not those kinds of things. It just was not the kind of science I was interested in. In terms of the memory, absolutely. My memory is not good for little facts. I suspect I would have done terribly in medical school and wouldn't remember which patient was which, if I had gotten out. But we never got to that stage.

JG: You attend Radcliffe College?

SG: Yes.

JG: What was it like in the mid-1960s?

SG: Well, Radcliffe was a little schizophrenic at that point. The dorms, the admission, the administration that gave you advice on what to take were all specific to Radcliffe. But all the classes were co-ed with Harvard. So there were about five Harvard men per one Radcliffe woman undergraduate in any class. So we had a good time. [Laughs] It was very nice. I was living in the Radcliffe Quad, which is now considered sub-standard housing because it is so far from Harvard. In terms of the courses I could take they were everything and they were great. There were not so many women around in some of the science courses. I got a lot of attention. There were places that were not perfect in a sense. I think some of the courses I chose to take as a freshman I would not have chosen if somebody had given me better advice. As I said, I was interested in physics and at Harvard there were multiple physics tracks. There was this sort of standard one for biochemistry majors, which is the way I was headed. Then there was the hyper-physics course that was for the people who were going to end up being physicists. I went into that but it was very clear very soon that I did not have the math to support it. I went in thinking I could do anything, I could go any direction, and I was a little surprised in how some of my classmates at Radcliffe had much narrower views of their own life. So even though they were highly selected, they were all smart, they had done a lot—many of them came in thinking they would get married and have a family and not necessarily do other things. There were not a lot of women faculty members but I am not sure I even noticed that. The president of Radcliffe at that point was a woman named Mary Bunting, who was a microbiologist actually, not that that had connected with me when I applied or anything else. There were freshman seminars which were small groups run by people on topics that they were interested in. She ran a freshman seminar on microbiology that I applied for and was able to join. So that meant that we had a little lab that we could play in, and there were four of us, that were freshmen, that spent some time there freshman year doing experiments, and meeting some senior scientists who came in to give us advice on what we were doing. There some older undergraduates who were sort of overlooking things. Mary Bunting was not around all that much, because at that point she was also on the Atomic Energy Commission. She was in and out of Washington, as well as being president of Radcliffe. But that was a very useful experience and sort of kept me close to the petri dishes.

JG: How do you think the Radcliffe experience influenced your career later on?

SG: It certainly in the end exposed me to a lot of terrific science. I had worked in Jim Watson's lab. I am not sure how useful that was in terms of him specifically, but I met a lot of other scientists who have been my colleagues and some I have remained close to. In biochemical sciences they had a tutorial system. So this was, again, Harvard specific, not Radcliffe specific. It was the place as a whole. The tutorial system meant that someone was going to be my tutor and I would meet with them from probably sophomore year, but certainly junior year on. We would meet and discuss readings or something and then I did my senior thesis with them. That was Boris Magasanik. It turned out that for me—I don't know whether somebody carefully matched us—that he was a microbiologist. He did beautiful work just in the kinds of fields that I was interested in. So having him as my tutor, being able to work in his lab, meeting him and people at MIT, getting advice from him on where to go to graduate school, all of those things were invaluable. Then there is Michael, who I met when I was a freshman, and who was going in the same direction, but more M.D. oriented. Obviously because we got married in my junior year, that had a big effect on where I was going to go geographically.

JG: You start Radcliffe in 1963 and are there until 1967.

SG: Right.

JG: What is going on culturally during that time?

SG: Yes. [Laughs] Well, it was on the edge of the place exploding. It got more so towards the end and after we left. Partially because I got out of the dorms when I got married I was not in the middle of some of it. First of all, the way the place was set up changed a lot between mid-1960s to the end of the 1960s. Radcliffe when I started there were sit-down meals at dinner and there were things you were not supposed to wear. You were supposed to be there on time, sit down, and then be served dinner. If you were not there at the right time you did not get dinner. That slowly disappeared. Not that many years later the housing went co-ed, a number of years after I had left. I do not know exactly when that was. There were rules about visiting. So we could visit the Harvard dorms only between four and seven in the afternoon. Which meant that you would miss dinner if you were there until seven. Then there was the Vietnam War. Things were starting to heat up towards the end. The place became much more politically active. A lot of that was not going on so much in the first part, in the part when we were still undergraduates, it is more a part of when we were in graduate school. Then it was more obvious. But things were changing. There were—what did they call them? Jolly-Ups, the dances, the social dances that Radcliffe organized, were called Jolly-Ups, and people came to them. People reported meeting Jim Watson there. And he said he was a professor, and they did not quite believe it. So it was an interesting place, but it was changing.

JG: You apply for an advertisement—

SG: Yes. So, freshman year I was working in the lab because I was doing this freshman seminar. And after that I missed it. I missed being in the lab. I looked around and they were advertising for part-time, specifically Radcliffe undergraduates, to work at the BioLabs. It turned out that it was Jim Watson's lab. So I had a short interview with Jim Watson who basically said, "Well, you won't get to do your own experiments until you are well into graduate school." He basically hired two or three of us to work as technicians for a graduate student in his lab who was finishing up. I was there some of the time and the others were there other times. I did various things, nothing terribly exciting—TCA precipitations and various other things—but I enjoyed being in the lab. The guy I was working with, Gary Gussin, has remained a friend and a colleague. We were in the same room with Mario R. Capecchi who has done extremely well since then (he won a Nobel Prize). Every day at four o'clock there was tea, and while I guess I was not brash enough to sit at the scientist table, I ended up sitting at the technician table. I got to know a number of other people who I have remained close to. Joan A. Steitz who is at Yale, and is very well-known, probably was the only woman around there at that point.

JG: What were your impressions of Watson at that time?

SG: Well, I also took his course. He taught a couple of courses. In his course, first of all, he mumbled. You could not hear him half of the time. What he did have to say was usually sort of digs, nasty things about various other scientists. So it was entertaining, but a little odd. I was interested in molecular biology so I took his course and I took Wally Gilbert's course. I took a lot of the basic stuff. But I am not sure I exactly saw Jim in terms of a personality. He was clearly strange. I mean he was dating undergraduates at that point. I was not in the lab enough to get the sense of some of the other things that were very positive about the lab in terms of how things got done so well there. I did not realize until after I left some of the way he handled things. He did not put his name on the papers of any of those people. All those guys that were in the lab then, that I got to know; they published important papers without his name on it and instantly became famous. He was in fact a very supportive mentor. There were other people on this campus who were in the lab then. Bob Weisberg, who just retired and will be working over here with Sankar in retirement, he says he is going to come over here to do a postdoc, he was an undergraduate working in Watson's lab, but not as a technician, doing an undergraduate project then I think. He credits Watson with keeping him out of medical school and having him go on to graduate school instead.

JG: You graduate magna cum laude from Radcliffe College. What were your aspirations?

SG: I just assumed I would go on to graduate school. I would get a Ph.D. and I would run a lab. [Laughs] It just did not occur to me that there were really other options. Things seemed less complicated, and that somewhere along there I would have kids.

JG: You decide to stay at Harvard?

SG: Well, yes. So this is Michael basically. We were married during my junior year and he was a year ahead of me. He was applying for and going to medical school. His first year of medical school was my senior year of college. When he looked at medical schools he looked at Harvard, and a little bit at other places, and for a little while I was looking at whether I was going to need to transfer. In the end he stayed, he went to Harvard Medical School, so he had a little bit of a commute, but that constrained my options in probably a useful fashion. That is, I really was only looking at graduate programs that were around the Boston area.

JG: Did Michael have an interest in being a physician?

SG: No, he was always very research oriented. He had done research in high school. I think he might have published a paper when he was still in high school in the New York area. He had had a tutor in biochemical sciences and had done some research as an undergraduate. Then in medical school he ended up doing a fair amount of research also. I do not think he ever imagined he would be practicing medicine full time. I am not sure that we had discussed exactly what the mix was but he was research oriented for sure. So anyhow, I talked to Boris Magasanik about where should I go for graduate school and basically his thoughts were in terms of specific people around the Boston area. The two people that he mentioned who were both doing really state-of-the-art research, had just come back to Boston, were establishing labs, and doing exciting work, were a guy named Ethan Signer who was at MIT and Jon Beckwith who was at Harvard. Because Boris was at MIT when I was at Harvard, I had done my senior thesis research in his lab at MIT. So my senior year, I spent a lot of time at MIT. I was more interested in Jon.

JG: Describe Dr. Magasanik. What type of researcher or scientists is he?

SG: He comes to research from a microbial physiology background where he probably knows more about the bacteria and how it actually deals with its environment than many other people. He was moving into much more molecular biology kinds of approaches in regulation. What can I say? The course he taught at MIT I could not make heads or tail of when I took it. [Laughs] He used a very dense book called *The Bacteria: A Treatise on Structure and Function* that had these chapters full of all the intermediary pathways and how things get metabolized that you see up on walls sometimes. Which bacteria did which parts of that, and how they did it, and things like that. It just went through my head mostly. I took it as an undergraduate . . . I went over to MIT and I took it. When he tells stories in seminars, the stories are amazingly clear. He was interested in nitrogen regulation. He had been interested in catabolite repression. The standard reaction to Boris is you hear him give a seminar, and he never used slides, he would always just write it on the board, even after everybody else was using slides. He is now emeritus, but is still around. It would all fit into a beautiful story. Sometimes it was a little hard to reconstruct afterwards, but while you were listening it was great. He was a tutor though for a lot of people. He did this, I do not know whether he is still doing it, but he was a tutor before me. Of the people I have encountered, who he was also a tutor for, is a scientist named David Botstein. He is now at Princeton; I ended up working with him later, and he is a really world-class scientist. Magasanik was still acting as a tutor a generation later when my son was in college. A friend of his was a tutee with Boris and she worked with him too.

JG: Was he skeptical/creative as a scientist?

SG: He is certainly creative. I am not sure I would call him skeptical exactly. I am trying hard to imagine how I would capture what he has done. He had a lot of very good people. He used genetics and physiology to figure out regulatory networks, which in a sense, is what I ended up being interested in. He used a lot of different approaches and put together stories.

JG: How about Dr. Beckwith? What type of scientist is he?

SG: So Jon has a whole book that will tell you about what he thinks of what he has done. When I got to the lab it was a relatively young lab. He had been back from his postdoctoral fellowships in Europe for a few years—had gotten the lab started. The first batch of students was already through there. He uses genetics in amazingly creative ways. The highlights of his career through the years are how you can query very complex questions with genetics. What he had done in his postdoctoral work in collaboration with Ethan Signer at MIT had been to work out ways to make bacteriophage lambda do what you wanted it to do and pick up bacterial genes. My thesis was a continuation on that. What was going on in the lab at the same time were experiments on regulation and how regulation occurs. It turned out to be in direct competition with the guys here in the LMB at NIH. But that is a separate issue a little bit. That was not my project particularly. After I left he sort of totally changed directions, got tired of that, started using genetic methods to figure out how proteins move from inside the cell to outside the cell or to different compartments in the cell. He made a whole series of critical contributions. There are always interesting things going on in the lab. He is also very politically active, left-wing politics. So there was a lot of that going on in the lab too.

JG: You were there doing your doctoral work between 1967 and 1971 which is a very political time. Can you talk a bit about that?

SG: Well there are various levels of politics. The Vietnam War was heating up and there were the usual—we have pictures of ourselves—at rallies and things like that. I also think we were a little busy. We did not get quite as involved in some of that. There were other levels of political activity. The civil rights movement was going on. That was going on when I was in college. We were down here for some of the marches. That was stuff that I started in high school. I also think we were a little bit removed, being one, Michael was in medical school, two, we had our first child in 1970. That kept us a little bit busy. The other thing that was going on in the lab I was in, in Jon's lab, was that they put together—this was pre-recombinant DNA, they used lambda in a way to isolate a pure gene. You get one piece of DNA that carried one gene. Which was fine, it allowed them to do some experiments they wanted to do, and that is why they did it in the first place. But they used it as a platform to talk about the uses of scientific information and the implications of being able to manipulate things. They made political statements about it. It was chaos there for a while. They ended up in the newspapers and lots and lots of publicity about how this was going to change the way everything was done.

JG: What lessons did you learn?

SG: Well, you have to understand that we have not talked about my political, or my parents political background. It is pretty left wing. So I was sympathetic but not involved myself in this thing. In general, I think Jon usually has some reasonable basis for his political stances although at various times through his life it has gotten him into trouble and really annoyed people. While I was in the lab, I think he got the Eli Lilly and Company Research Award, which is a big award. It was from ASM, the American Society for Microbiology, for the best science by a young scientist. It is usually a presentation of your science at the annual meeting. What he did was . . . He may have done a little bit of science, but most of it was a political speech and he said he was giving the money to the Black Panthers. I do not think it was a lot of money, but there was a lot of this going on, and it just made people mad most of the time around Harvard. Harvard Medical School was not the most left wing place in general. I was probably more sympathetic than I might have been if I had come from a different background. Later on when I got very involved with recombinant DNA I was interested in getting Jon enough involved so that we could hear what he had to say in terms of the science and really take account of it.

JG: What did you learn as a doctoral student? How did these techniques prepare you—

SG: I am not sure. [Laughs] One thing was that you could do practically anything with genetics and that you could manipulate the system to get it to do what you wanted it to do. Then I think the way that questions were being asked at that point was take it apart into specific steps that you could look at in detail and how to do that. It is all sort of logical thinking and . . . In terms of techniques I got to know how to do a lot of bacterial genetics. When I came here to a place that was mostly sort of phage-oriented I was bringing the bacterial genetics with me to some extent. In the end, that has been the basis of research that I have done. When I came I had in mind that I needed to know more about phage, because phage were one, interesting scientifically, but two, were a tool that I could use in the bacterial studies, to go back and forth.

JG: Talk about the difference between bacterial genetics and the phage genetics for a lay person.

SG: Well, the phage depends on the bacteria. The phage is growing in the bacteria. At that stage, working with bacteria, we have this big genome, full of lots of genes. We did not know what they all were. We were still trying to figure out what it could do and how to query it and how to make a strain different from the strain that you had by one change, so that you could find out what that change did. There were some techniques that were available at that point, and now, you know, they are just so advanced that you can do anything basically. What might have taken us weeks or months now you can do in a couple of days. The question was how can you take the bacteria . . . Let's say I have a mutation. Let's say this bacteria used to grow on this Petri dish in one fashion and now it looks somehow different and I want to figure out what gene is doing that. How do I figure that out? How do I move it, figure out where it is on the bacterial DNA chromosome. There are ways to mate it, and look at when that gene moved, and what its properties were when it moved. Is it one gene that is causing the change or multiple ones? Everything is very indirect because you are basically manipulating colonies and looking at the outcome. The phage, at that point, you would be looking at plaques. You would be growing the virus on a bacterial lawn and looking at whether it grew or not and taking it out and moving it to another bacteria and seeing how it behaved on a different bacteria. It was easier to manipulate the phage because it was easier to move it from place to place. People used it to isolate lots and lots of mutations in the phage and then start to dissect what they did. But the fields are not totally different. The phage were also a tool to do bacterial genetics. The genome is a lot smaller, so easier to analyze. You used phage in various ways. I'm not sure that is helpful—

JG: You published your first article while at Harvard. Talk about that experience?

SG: This derived from the work that Jon had done originally which he had figured out. That paper became obsolete not too many years later. That is the first thing. The idea was to get the tools to study bacterial genes and to use phage to do it. What he had worked on when he was a postdoc was how to put the bacterial phage lambda which integrates into the bacterial chromosome next to the *lac* gene and then it would sometimes pop out carrying *lac* with it. Then you would have, instead of having this particular *lac* gene one in four thousand genes, it would be one in a much smaller piece of DNA and you could try to do biochemistry and other kinds of things with it. My project was to try to accomplish the same kind of thing for another set of genes called the arabinose operon. The arabinose operon was interesting because in the first molecular biology understanding of how regulation occurred, *lac* was the primary case and we knew that was negatively regulated—a repressor sat on it and kept it from being expressed. Arabinose was supposed to be positively regulated. Somehow something positive happened when arabinose was around to express these genes. But it was not at all clear how it was working. There was some genetics on it—some mutants that had been isolated. But in order to look it, and try to get the proteins out, and try to look at the protein-DNA interactions and all of those things, we would have to have some way to get those genes. My project was to use basically a protocol that Jon had already put together. I had to make it work, but it was sort of handed to me, to put lambda or a lambda derivative phage next to the arabinose genes and then pop out the lambda and bring the arabinose genes with them. That is called a specialized transducing phage and that paper was to isolate a specialized transducing phage for the arabinose operon. Once you had recombinant DNA, a few years later, there were easier ways to do it. At that point it was useful and I made it. So that was sort of what was supposed to be part one, was making this. That happened fairly quickly and then possibly using that to try to isolate the arabinose regulatory protein and figure out how it worked, which didn't go quite as far, was the rest of the thesis.

JG: What was it like to have your first paper?

SG: My memory isn't good enough to remember. [Laughs] It was nice. I do not remember it as being world shaking in any fashion. I forget occasionally, that for our students, how nice it is to all of a sudden to finally have a paper. It makes the science somehow more concrete in many ways. It is there and it is there forever which is very different from the stuff you are doing in the lab and the notebooks and everything which all feels like it could come or go. So in that sense it is very nice. By the time I came down here to give a talk when I was applying for a postdoctoral position it was already obvious that stuff that was going on here had bypassed some of what I had done. So it was not the most earth shattering thesis in the world. But it got done and it got done on the four-year schedule with the child born in the middle that fit our family so it worked.

JG: What opportunities are you now looking at? You got your Ph.D. and what are your aspirations?

SG: Still, the idea of running a lab at some point. I do not know that I had a specific project or direction in mind. I just assumed that that would work and I would go and continue on and eventually be running my own group.

JG: You are recruited by Max Gottesman?

SG: No, no. I came to Max's lab, but again, I am geographically constrained to a large extent by Michael. Michael was one year ahead of me, so he finished medical school and did a year of internship. He is finishing his internship at the time that I am finishing my thesis. But we are looking for postdoctoral positions a year beforehand. This is mid-Vietnam War and there is a doctors draft and he has his M.D. and he would be drafted in spite of the fact that we have a small child. So given that, and given the fact that he was interested in research anyhow, the obvious alternative for him was to go to NIH and join, whatever it was called at that point, the U.S. Public Health Service Commissioned Corps. He is going to serve his military obligation in the public health service in place of being drafted into the military. He will be a research associate, come down and work in somebody's lab. He was interviewing for that and was accepted into that program. When I was looking for postdoc fellowships it was not look around the whole world and figure out the places I wanted to go—the question was, who at NIH would be good to work with. Maybe because of the name, or for other reasons, one of the names that came up all the time was Max Gottesman. In fact, Max at that point was still working with Michael Yarmolinsky. People told me to go talk to them both, but that Max was doing interesting stuff. I talked to a couple of other people. I talked to Phil Leder who had been doing some interesting things with *E. coli*—looking at translation. By the time I came and interviewed with him he was moving into eukaryotic systems and they did not interest me much, and I may not have interested him either, because I was still fixed on the bacteria. Max had a nice project that appealed to me in terms of he had this tool that allowed us to start looking at lambda site-specific recombination. That was a good match as far as I was concerned.

JG: Describe Max a little.

SG: Max is someone . . . [Laughs] I will describe some characteristics which maybe somebody else like Sankar [Adhya] described or maybe not. Max's idea of a nice experiment is one that you can do on one Petri dish. Basically you can see everything there. Think about it a lot. Figure out how everything works and how you can get the answer quickly. It is just all there. The other thing is that he likes to talk about science and think about science. So if you mention to him anything—you have a result that is interesting—someone on the other side of the country will have heard about it before you have had a chance to finish the thought practically. It was a great, in general NIH was a great environment for what I was doing. It was not just Max it was a whole community of people. Max was tolerant. When I came, when I first arrived, I was still trying to fool around with the arabinose operon and my transducing phage and try to see whether I could purify the protein and he tolerated me doing some experiments like that for a few months until I got disgusted with it and left it behind and really got into the lambda stuff. Half the time I do not actually know what he is thinking. In fact, it was a very active scientific group and a much more interactive group than I think Jon's lab was in the sense that there were a lot of senior people here all talking to each other all the time.

JG: Describe Bethesda in 1971 or 1972 when Michael and you arrive at NIH?

SG: We were living just outside the Beltway off Democracy Boulevard in some little house. Across Democracy Boulevard were fields and cows where there are now shopping malls and various things. I think partially there were fields and cows there because someone was getting a tax break to keep it agricultural. We considered it, in a sense, the South. Bethesda, downtown Bethesda, was not at all high rise. There was nothing over two stories. There was one Chinese restaurant, one Italian restaurant, a couple of seafood restaurants. There was no subway downtown. It was different from what we were used to. It was hot. We arrived in the beginning of July—Michael's year was July 1 to July 1, so we arrived in July—and it was like nobody lived there. Nobody was outside; it was hot and humid. The NIH community was sort of a different world to some extent.

JG: When did you meet Ira Pastan?

SG: Probably not that long after we came because Michael Yarmolinsky had left for Paris. He was going to move his lab there. Max had his own group. They must have been already starting to interact with Ira at that point. So we started to have joint group meetings even before we physically moved over here to Building 37. Of course, there I was running into the competition between the lab I had come from and the lab here because they were both working on cyclic AMP and the receptor protein for cyclic AMP. In fact, Ira had come down and talked to Jon about how to look for it genetically. Jon had this beautiful genetic screen to look for mutations in this factor that they thought existed. They had found them and they had a different name for the gene there from here. The two groups had come to some disagreements. They were basically competitors and they were not that friendly competitors on that subject. So I sort of said, "Let's not talk about what is going on there." I wasn't carrying information from one place to another but I had to change what I called the protein because it was CAP there and CRP here and by what you called it you were declaring your loyalties.

JG: What do you think the aspirations of the LMB laboratory were and what were Ira and Max trying to accomplish when you first got here?

SG: It was in the early stages of being able to do biochemical studies of basic molecular biology questions. How cells do regulation and how genes are turned on and off. That was what they were trying to establish—the use of molecular biology and biochemistry to answer basic questions of regulation. I am not sure that I had a sense of the big picture exactly, but it is clearly where they were going. Other people were trying to do this also. They had put together a group. So the combination of Ira with his interest in cyclic AMP and Max who had a lot of this phage and bacterial genetics expertise and Sankar as well who had been working on the *gal* operon, was clearly aimed at building up a group that would have the tools to do some things that other people were not doing.

JG: It was a very young laboratory. In the pictures everybody is very young.

SG: I suppose so, right. I am not sure that I thought of that, per se. They were older than me at least. [Laughs] That was true of the lab I was coming from too, that people were young.

JG: Speak about Ira's concept of recruiting a group that had expertise in biochemistry and genetics. Were you aware of this strategy at the time?

SG: I had to sit through all these seminars. We had group meetings every week to hear what was going on. Some of that was biochemistry. I was more interested in genetics. That is the way I like to think about problems. But it was clear that to answer some of the questions at the level that they wanted to answer them you had to do the biochemistry. Some of the biochemistry took a long time. There were parts of it that sort of went off in random directions. It seemed more to me like phenomena than a clear story. Other parts were very successful and eventually gave us a much clearer idea of how things were going. I am not sure I was thinking about what he was looking for, or how he was doing this, but it was clear that the group was a sort of a mixture of approaches. Max is really . . . Max will interact with everyone about everything. He just gets involved in the science, whatever it is. He was a good person to have involved in that group, I think.

JG: Describe Ira as a scientist? Is he skeptical or creative—

SG: To some extent I have not interacted much with Ira directly on any of the science that I have been involved with. I have had less experience of seeing him think about things and how he dissects things. I am not sure I would call him skeptical. He is an empire builder partially. He sees chances to put together groups of people to answer questions or to solve problems. And he does that. He has done that with immunotoxins and he has done it with other things. Probably then was the time that I had the most opportunity to see him react day-to-day to what was going on and I can't say I have a clear image of his style with respect to that. I am not sure I am very useful in thinking of it. He does not necessarily think about things at the same level. He looks at problems entirely differently than the way I do. So we have not really intersected. Michael probably has more to say on this because Michael interacted with him a lot more on the MDR project.

JG: What was the NIH like for a young researcher? You spoke a few minutes ago about the community here—

SG: There were two kinds of communities. One was the phage community which still goes on in a group called Lambda Lunch that meets once a week and that I now help organize. That group was intensely interested in everything about bacteriophage lambda. They are all experts and already had a whole bunch of experience with each other so they talk to each other in a code. In terms of the name of the phage, they are color coded. I probably sat in the seminars for a year before I knew what everything meant that they were talking about. But they were excited about what they were doing. There was an incredible amount going on and that was the group that I interacted with most of the time. A number of them are still around here.

JG: They were from different parts of NIH?

SG: Yes. There was a group. Bob Weisberg was over in Phil Leder's lab in Child Health. He and Max had published together from, I don't know when on, they had interacted a whole lot. There were people working with Max. Don Court came to Max's group. Sankar was in Max's group. Lee Rosner was in that same building in a somewhat different group. He is still here. Probably Bob and Max were the major organizers of groups that were interacting at that point. Then other groups broke off from those at various points and went in various other directions. There were a few other people on campus too with different phages but not so much a part of this Lambda group.

JG: I know that later in your career you would teach some of the NIH night schools? Did you take any of the coursework at that time?

SG: No. I think we started teaching it relatively early on with Max and Sankar, me and Don Court who is now out in Frederick [Maryland]. We probably started that certainly late 1970s I would think. I would have to go back and check and see if I could figure it out. I do not think I took anything. I had taken a lot of coursework when I was an undergraduate. I basically took everything I could take and then on top of that I took the courses in graduate school. I do not think I felt the need to sit in a course at that point. Then in terms of communities there was the other sort of people in Building 37 and around the NIH. What was striking was that here, more than at Harvard certainly, there were a fair number of women scientists who were working on campus. So Maxine Singer was on the same floor we were on.

JG: Talk about Maxine Singer.

SG: I did not get involved in knowing her science so much but she was a very accomplished woman scientist who was right there and was always supportive and friendly and had four kids I think. So the issue of could you do science and have families seemed like something that . . . It always helps to have somebody around who has done it although you do not always know how hard it might or might not have been. There was actually a graduate student in Boris's lab when I was doing my senior thesis who I worked with who had a child while she was at graduate school. So probably some of those examples made it easier to have our kids early on.

JG: There are three of you now with the same last name and you publish a paper together?

SG: Right, right. [Laughs] Michael was working with Marty Gellert on a different project. I was working with Max so I had a bunch of publications then and later with Max.

JG: And is there any relation?

SG: Not that we know of . . . [Laughs] We haven't done DNA profiling. I am sure we could find something. If you ask Max he will tell you that we are all related to the Ur-Gottesman. He has a slide that he made at one point with the imaginary Gottesman genealogy. When we were in Building 2, I think everybody knew who we all were. When we moved over here, there were clearly people who thought that I was Max's wife. There were lots of people who were confused about who was related to who, and because I was publishing with Max, the assumption was that I was related to Max. Michael got some invitations to things that he assumes were for Max and I do not know whether Max got some for Michael. So there was a certain amount of confusion. There continues to be to some extent but it is mostly entertaining. Then Max and Michael started to collaborate on this project. So Michael was trying to isolate—we are still pre-recombinant DNA—a gene called ligase. He was trying to get lambda to pick it up. He had a plaque assay that allowed him to look for lambda that had picked up this ligase bacterial gene using some techniques that had been developed basically in Max's and Bob's labs. Instead he picked up something else. He picked up something that they, in the end, showed was a piece of bacterial chromosome that had lambda-like functions on it. When they were doing this collaboration the possibility of putting us all on the paper did arise. What we were interested in was where did that bacterial piece come from in the bacterial chromosome and that was my field of expertise. So I did that part of the experiment so that we could have that Gottesman cubed paper.

JG: I read that it was an effort to show that there just wasn't one Gottesman that was extremely productive.

SG: Yes, you are right. [Laughs] There is no question that people would think that Max had done everything that Max and Michael had done or that Michael had done everything Max did. They just did not realize they were two people. I was a little bit less . . . I at least had a different initial, and was a different sex, so if they had met me they would know I was not Max. But for Max and Michael it did help to prove that there were three of us.

JG: You leave NIH and go to MIT.

SG: Yes, again still moving with Michael, and with Michael's agenda to some extent, although it was not a real struggle for me. Michael had done an internship, but not a residency, before we came to NIH. He wanted to finish a residency and basically Harvard would give him credit for the years he was here so he ended up only having to do one year. So we went and he immediately did a senior residency. We went back to Boston with the idea that he would do his residency and then we would see. I needed a place to go and David Botstein who had I had met as a graduate student and had been on my qualifying exam came to my defense. He said he had space for me and I could come and do whatever I wanted. He offered me space and salary and said, "It would be helpful to have you around the lab but do what you want to do." I brought my project with me. That was one, a great environment, and two, a terrific opportunity to keep working on what I was working on which in the end developed into a major change in direction that I put into place later.

JG: Describe what it was like to be at MIT in comparison with NIH, and also with Harvard?

SG: Well, it was a very high power place at that point. David's lab was partially in transition, starting to work on yeast and continuing work on a phage that grew in *Salmonella*, a bacteria closely related to *E. coli*. They had similar but parallel interests to what I was doing. I had been around MIT a bit. I had done my senior thesis there, so I knew my way around. Boris was on a different floor. The woman that I had worked with as a student, that had been in his lab, was back there. It was a much more competitive place than NIH felt like. That is, there were a lot of little fiefdoms each trying to make a name for themselves. It was also a lot of good science. The lab I was in had a bunch of postdocs, or people basically in my position, plus or minus a year or so, who were doing very good science that impinged on what I did in many ways. Even though I was doing my own project I started using tools that Nancy Kleckner developed while I was there. We have continued to collaborate a little bit on those. She was looking at genes that hop around, transposons. She was interested in the mechanism of transposition but she was also making some tools for how you could use them for bacterial genetics and I was doing bacterial genetics and then sort of putting them to use very quickly. So that sort of jump started some of the genetics that I wanted to do because I had these tools at the very beginning of their availability for the field. It was a still a very male dominated place in terms of the faculty at MIT. They were all getting divorced, I think. It was not a stable . . They were not all happy campers exactly. It was an interesting place. [Laughs] I like MIT and I have very good colleagues there now. We had a much better view than in this building. You are not seeing this building as it existed originally. This building has been entirely renovated. In its original version there were windows around the very outside and corridors through the middle and all the labs were off the corridors of the middle. So none of the labs had windows. If you wanted to know what it was doing outside you had to walk out of your lab and walk down to the end of the corridor and look out or have somebody call you and tell you, "It's raining, it's snowing, something's going on." At MIT my bench was a big picture window overlooking the Boston skyline so it was very pleasant.

JG: What type of experiments are you doing there?

SG: I took back with me the lambda site specific recombination project that I had been working on with Max. We were trying to move it *in vitro*. The idea was to get this recombination reaction to go *in vitro* and I did some work trying to isolate the proteins and get them to work *in vitro* in various ways. One of the side projects that I got involved with derived from work by Max and [Robert] Weisberg. They had published a paper in 1971—so I knew about it when I was here but I had not really followed it up—that said that the site specific recombination reaction is a phage recombining with the host chromosome to integrate itself into the host chromosome and then it was a reversal in which it excises itself. It was the excision reaction that I was working on. We knew that there was a protein that was used in both directions and then there was a special protein that was used to bring it back out called Xis. They had a paper showing that functionally that protein was unstable. If you made Xis in the cell, and then asked about its activity over time it disappeared very quickly while the protein that let it go in or out (IAT) was stable over time. There was some biological explanation for that but nothing known about how it disappeared.

What I was trying to do is purify these proteins and get them in enough quantity to make it work *in vitro,* which we got to, but it has not really turned out to be my field of greatest accomplishment. The fact that it was unstable meant that it might be harder to find it. A paper got published describing some mutations that seemed to be in a protease, in an enzyme that would chew up proteins. I got interested in starting to look at that mutation to see whether it would help me make that protein Xis in more quantity. The original idea was, "Okay, if we can block the protease that is chewing it up it will be easier to purify it." I got those strains and started to work on them. They were a mess genetically. The way they had been studied did not really dissect them out into single mutations totally. The phenotypes were hard to study and I did not want to have to do the hard experiment so I started to think about how can I test whether the protease is there or not in a simpler fashion. I ended up collecting temperature sensitive phage to use as a test for whether the protease mutant was there or not and I collected phage from a bunch of labs at MIT. It was certainly a rich environment for getting all kinds of tools. John King was working on T4 phage and had temperature sensitive mutants. Nancy Kleckner had done her Ph.D. on lambda replication and had temperature sensitive mutations in lambda. The idea was that the temperature sensitivity of phage growth might be due to proteolysis of a mutant protein, and might be suppressed by mutating the protease. That turned out to be true. I used these mutations and then started to dissect out the strain and figure out what was going on with it.

I did that as a collaboration with David Zipser who had published the first paper on these mutants but was not at MIT. Basically I did a lot of the genetics and he did some of the checking after I had made the mutant strains. As soon as I started to work with this mutant I became very interested in the fact that it had a lot of phenotypes, that it did a lot of things to the cell, and started to think about how to dissect those out. On the one hand I was trying to do the biochemistry of recombination and get the proteins; on the other hand I started to work on this protein turnover and its implications. I am not sure I published a whole lot while at MIT, probably just the paper with Zipser. I don't remember.

JG: You decide to return to NIH?

SG: It was always a temporary position—this position at MIT. Michael had done his residency and had gotten a soft money position at Harvard in the anatomy department in a collaborative project with Burt Vallee who he had worked with as a medical student and Judah Folkman who was interested in angiogenesis and who just died this past year. A really amazing guy. Anyway, they had a lot of money and were supporting Michael. Michael started to get into somatic cells genetics, he had been working on bacteria at NIH, but he was getting more into eukaryotic cells. So we started the process of looking for two jobs in one place. He had something in Boston. I applied for a number of places and then I guess Ira got some new space. He basically took over another lab and got a lot of extra space. I guess probably Max was interested in getting the site specific recombination project back. I had basically walked off with this project, which isn't always possible. They were obviously generous about letting me carry this off and this is one way to get it back—is to bring me back. I remember talking to Max at a scientific meeting and saying that I was interested in coming back. Ira went further than that and came up with a position: "Oh, Michael isn't doing bacteria anymore? He is doing something that is interesting to me?" So they offered us two positions. We knew we liked being in Bethesda. We knew it was a good scientific community. Two positions like that, which were like tenured positions at that stage in our career, were perfect. So we came back. I had a job offer from Michigan and Michael was not really interested in going to Ann Arbor. I had looked at more sort of research associate positions at MIT, not with David, but with one of his colleagues as a backup. We were sort of looking around but this made it easy.

JG: How had the laboratory changed in the two years that you were gone?

SG: Not a lot, I don't think. I don't know. I was in a different room probably. When I came back I had a room that was my room basically that I was setting up. I am not sure I remember what was going on before and what was going on afterwards. My visual memory is of this building and that fourth floor and conference room and what was going on there. Exactly which was happening before I left, and which was happening after I returned, I would have a hard time telling you, unless I went and found my notebooks and looked at what I wrote down.

JG: During the 1970s you have the recombinant DNA controversy. Talk about that controversy and how you become involved, and also your work with Nancy Kleckner on drafting the guidelines?

SG: Yes, okay. I was at a Gordon Conference in which I heard Herb Boyer first present a talk about the recombinant DNA, the process, what you could do with a restriction enzyme and how you could put together new pieces of DNA. People got very excited about that. Obviously first it was being done entirely in *E. coli* which people had just learned to do. Pretty early on the issue came up of what could you do that you really don't want to do? What missteps could you take? A lot of it was in the context, I think, of the atom bomb and what had been done with the physics and how it had gotten out of hand and been used for weapons or used in various other ways. It was in that political context that biologists seemed to think they wanted to get a handle on it early on. They brought up these problems and said, "You know, we're going to look at it, at the first step." Of course, Maxine [Singer] and others, out of a different Gordon Conference, first proposed that there should be some brakes on how this was done. Then there was Asilomar [Conference on Recombinant DNA]. We were doing our science and not using those techniques yet at that point. We were aware of it. The question was should one really be concerned? Most of the concerns had to do with safety rather than deliberate misuse. You were putting DNA from two places together, you did not know what they were, what was going to come out of it? Add to that the fact that there was really in our field very little history of being careful. I mean we were working with non-pathogens; we were working with things that did not cause disease. None of us were trained to necessarily be careful about what we handled. You could imagine that people could make things they did not intend and that they would be out in the environment before you knew about it. There was some background concern about deliberate misuse. I think those were things that someone like Jon Beckwith had been warning about it and was particularly concerned about. There was a lot of controversy going on in Boston and then every place else about what kinds of precautions should be used.

JG: Cambridge?

SG: Yes, that may have been a little bit later. Nancy Kleckner and I were both in David Botstein's lab as postdocs and one of the early meetings of what was going to be the recombinant DNA committee was taking place in Boston, probably in Cambridge, because I don't remember going much of anyplace for it. They had put together some early rules saying there will be physical containment. You will keep these things in some kind of container and safeguard them. Then there will be biological containment. You will design them in some way that they are not going to get out and grow. One of the committees was supposed to look at phage and how they would be contained. The question was you were taking your piece of DNA that you were interested in and you were putting it into some kind of backbone and the two kinds of backbones that were being used were plasmids and phage. We were a phage lab. We knew a lot about phage. David's lab did and I did from what I had done before. David was invited to sit on this subcommittee to look at these proposals for safe phage and safe plasmids and he wasn't available and he sent Nancy and I to go sit there. We did not entirely agree with what was being presented.

JG: How so?

SG: Maybe because I was out of Jon's lab and he was very skeptical about the whole thing. Or, you know, just in general, if you were going to say that you wanted it contained. There were people who did not think it was dangerous. There were people who did. We were just sort of saying, "Okay, if it is going to be dangerous, what is the containment?" I think the presentation that we were given was that you were going to contain the phage, keep it from spreading by using chloroform or something. It just did not fit entirely what we thought was appropriate. So we wrote a minority letter disagreeing with the committee. In the end additional safeguards were added to these vectors in terms of how they would grow and how they could not grow in the outside world. They ended using mutations in the phage so that it could not replicate except in a special host, basically. That was at the point where I must have already known I was moving back to Maryland and the guys who were administrating that committee and were sitting there realized that they had somebody around the corner who had some opinions and wasn't afraid to state them. They ended up sort of dragging me into a lot of the recombinant DNA work on this campus, so that the committee was meeting a lot, and eventually revising the guidelines entirely, trying to figure out how you classify what bacteria are safe to work with and what ones aren't. I had to learn a lot. It was beyond the *E. coli* that I had been sort of brought up with. I had never worked with anything other than *E. coli*.

JG: Can we go for about another five minutes? What did you learn about the creation of public policy?

SG: Yes. Well it was an interesting exercise. What did I learn? It is very complicated. This committee was in a sense unique in that it was meant to have both public members and scientist members. It is very hard for public members to listen to scientists and know what to make of it. I mean, I think that was clear. They sort of learned, some of them learned a lot of the science, others learned who they trusted and who they did not trust in terms of what was going on. Scientists always want to do their experiments and there were a lot of good experiments to be done. There was a real tension between having enough safety to satisfy the critics and letting the science go on. NIH people were sort of anti-regulation. [DeWitt] Stetten who was chairing the committee at that time thought it was crazy that we were adding all this bureaucracy to science. It is difficult. I think after a lot of ups and downs, and a lot of time where people were very unhappy, we ended up with something that was workable for everybody and hit a reasonable medium. Getting there was not easy. It took a lot of time and energy and there were periods of years where the rules were sort of set in stone and you could not change them and science was changing much, much faster than that. So people could not do the work that they wanted to do. Then there were all kinds of interesting aspects of it. If you were talking to Congress, or anybody downtown, the most useful thing you could say is some other country will get there first. In terms of them stepping back and saying, "Oh, we have to do this," it was, "What's the competition out there." I learned a lot about the news media and which ones got things right and which ones didn't. For the first time I was seeing something I was involved in appearing in the newspaper or the news magazines. Sometimes it didn't bear any resemblance to reality. Some places are pretty good about getting it right. If the same percentage of what you read is right for everything else it is a little disturbing. Then I met a lot of interesting people with different, very different points of view that I might not have met otherwise. We spent some time arguing because I was to some extent the person that was pushing regulation on this committee for many years.

JG: Let's leave it there and pick it up again tomorrow?

SG: Okay. All right.

JG: Thank you very much.